# Evaluation of stress hormones in traumatic brain injury patients with gastrointestinal bleeding

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【**Abstract**】**Objective:** To evaluate the local risk factors of traumatic brain injury (TBI) patients developing gastrointestinal (GI) bleeding during the early hospitalization in neurosurgery intensive care unit (NICU).

**Method:** From September 2005 to February 2006, 41 patients admitted to NICU and 13 healthy volunteers were involved in our study. Blood samples at 24 hours, 2-3 days and 5-7 days were obtained from each patient via arterial line at 8 a.m. to measure the concentrations of serum adrenocorticotropic hormone (ACTH), total cortisol and gastrin. The collected serum was immersed in an ice bath and tested by the Immulite 1000 systems. Data were analyzed by SPSS 11.5.

**Results:** Within 24 hours following TBI, the concentrations of total cortisol, ACTH and gastrin increased proportionally to the severity of injury, especially significant in the experimental group ($P$<0.05). The concentrations of ACTH and gastrin were higher in the GI bleeding positive group than in the GI bleeding negative group, ($F$=1.413, $P$=0.253) for ACTH and ($F$=9.371, $P$=0.006) for gastrin. GI bleeding had a positive correlation with gastrin concentration ($r$=0. 312, $P$<0.05) and a negative correlation with serum hemoglobin (Hb) ($r$=-0.420, $P$<0.01). The clinical incidence of GI bleeding was 24.39% (10/41) in the experimental group. Within 24 hours, GI bleeding had a strong correlation with gastrin concentration ($OR$=26.643, $P$<0.05) and hematocrit (Hct) ($OR$=5.385, $P$<0.05). High ACTH concentration (>100 pg/ml) increased the frequency of GI bleeding. For patients with severe TBI and treated with routine antacids, the incidence of GI bleeding was 40.91% (9/22) and the mortality rate was 20%(2/10).

**Conclusions:** Low Glasgow coma scale scores, low Hb, high concentrations of gastrin and ACTH (>100 pg/ml) are risk factors and can be predictive values for post-traumatic GI bleeding. Severe TBI patients have high risks of GI bleeding with high mortality.

**Key words:** ***Brain injuries; Gastrointestinal hemorrhage; Adrenocorticotropic hormone; Gastrins***

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Traumatic brain injury (TBI) results from an external mechanical force applied to the cranium and intracranial contents, leading to temporary or permanent impairments, functional disability or psychosocial maladjustment. Road accidents in the world are estimated at 1 000 000 persons/year and at around 100 000 persons/year in China. TBI appears with a great incidence from 52.6% to 62.76% in all traumas, and with high mortality in severe brain trauma from 50% to 70%.[1]

Traumatic brain syndrome (TBS) presents with the primary injury during the acute period, which occurs at the moment of trauma and manifests as focal injury and diffuse axonal injury, and then the secondary injury, which occurs immediately after the primary injury and produces effects that may continue for a long time.[2] The primary insult induces the hyperadrenergic response that may be a factor of many complications.[3,4] The secondary injury brings the subacute period, combined with a lot of endogenous systemic alterations in the brain and the hypothalamo-pituitary-adrenal (HPA) axis, which induce many neuroendocrinological dysfunctions,[5,6] leading to changes in the amplitude and frequency of hormones secretion during acute stress.[7]

In the acute period, the secretion of adrenocorticotropic hormone (ACTH), total plasma cortisol and catecholamines[6,8-10] increases rapidly and correlates with the severity of head injuries, and the magnitude and duration of adreno-cortical responses.[6] But lesions occurring anywhere along the HPA axis pathway would disturb the normal HPA axis's secretion of hormones

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and interrupt normal inhibitory mechanisms, leading to abnormal amounts of acid secretion, and consequently to gastric erosions. Cernak et al[11] reported an early rapid increase in plasma cortisol followed by a period of hypocortisolaemia between Day 1 and Day 3 after injury, and then a second peak on Day 5 followed by a gradual decline.

Body's protective reactions to stress attacks are general and can induce a lot of impairs. Stress bleeding ulcer in patients with head trauma correlates with the severity of injury, and leads to high mortality rates regardless of presence of other risk factors.[12] Severe head injuries with the Glasgow coma scale (GCS) scores≤8 can lead to gastric acid hypersecretion and hemorrhage rates over 17%.[13] Autopsy studies revealed a double incidence of hemorrhagic ulcers in patients who died of central nervous system diseases (12.5%) compared with patients succumbing to non-neurosurgical diseases.[14]

But the relationship between hormonal change and GI bleeding is not explored at all. The aim of this study was to evaluate the association between stress hormones and gastrin in GI bleeding following TBI.

## METHODS

A total of 41 TBI patients injured within 48 hours, consecutively admitted to the neurosurgery intensive care unit (NICU) of Tianjin General Hospital and 13 non-stressed healthy individuals, taken as the controls, were involved in a randomized prospective clinical trial. The TBI group was composed of 35 men and 6 women (male/female=5.8) with the mean age of (34.84±15.72) years and the median age of 36 years (range, 16-69 years). The mean age of the controls were (43.92±14.68) years. During the period of study, the GCS scores of the TBI patients were between 3 and 15.

Patients' data consisting of age, sex, blood pressure, GCS scores, Marshall computer tomography classification (MCTC) were included in the trial to evaluate the incidence of GI bleeding. The mean time between injury and admission, the causes of TBI, and the Glasgow outcome scale (GOS) classification for one month were analyzed. But patients were excluded from the trail if they met any of the following criteria: inability to obtain informed consents from them or their relatives; therapies known to affect ACTH secretion or cause GI bleeding; being unlikely to survive; the presence of seizure, cerebral neoplasm, cerebral abscess, meningitis, encephalitis, suspected or radiologically proven facial fractures, or disorders of temperature regulation; having surgeries recently or case history of bleeding and/or varix/hemorrhoids; receiving treatments with steroids drugs (glucocorticoid or mineralocorticoid) within a month; or being resistant to H2 receptor.

### Techniques for blood sample collection

Every time, 5 ml blood sample was collected from each patient in EDTA tubes by venopuncturing into the vein of the left or right arm on the 1st, 3rd and 5th days after they arrived at the NICU. Sample collection was precisely timed at 6 a.m. to 9 a.m. to coincide with clinically indicated blood ACTH tests. To minimize intervention and reduce the risk of infection, sampling was avoided when patients had been disturbed all night by other interventions. The tubes were marked with time and immersed in an ice bath following collection. After centrifugation at 1500 r/min for 10 minutes, plasma was separated from cells in a refrigerated centrifuge. Then the plasma was stored at -80°C immediately in plastic glass tubes.

### Detection of plasma ACTH, gastrin and total cortisol

We measured the concentrations of some plasma hormones, including ACTH, gastrin and cortisol by sequential immunoradiometric assay with the Immulite 1000 systems analyzer. Generally manual methods and data analysis by SPSS 11.5 software were used in this study. Before the assay, samples were moved to a refrigerator below 4°C. All precautions had been taken to avoid contamination and exposure to direct sunlight.

**Plasma ACTH** Plasma ACTH concentration was measured by sequential immunoradiometric assay with the Immulite 1000 systems analyzer. We quantitatively measured ACTH in EDTA plasma of the 41 TBI patients for three days. The analytical sensitivity of the Immulite analyzer was 9 pg/ml. The antibody was highly specific for ACTH. The mean concentration of plasma ACTH was 9-52 pg/ml in the morning and 0-50 pg/ml in the evening.

**Plasma gastrin** Plasma gastrin concentration was measured using the gastrin radioimmunoassay — sequential immunometric assay with the Immulite 1000

systems analyzer. We quantitatively measured gastrin in EDTA plasma of the 41 TBI patients for three days. The analytical sensitivity of the Immulite analyzer was 20 pg/ml. The antibody was highly specific for gastrin with a precision of 98.9%. The normal concentration of serum gastrin was<100 pg/ml.

**Plasma total cortisol** Plasma total cortisol concentration was detected by sequential immunometric assay with the Immulite 1000 systems analyzer. We quantitatively measured the total cortisol in EDTA plasma of the 41 TBI patients for three days. The analytical sensitivity of the Immulite analyzer was 5.5 nmol/L. The antibody was highly specific for total cortisol. The mean concentration of plasma total cortisol was 5-25 μg/ml (138-690 nmol/L) in the morning and 3-12 μg/ml (80-330 nmol/L) in the evening.

## RESULTS

### Ages and GI bleeding

Of the 41 TBI patients, 24.39% (10/41) developed GI bleeding. Four age groups were constituted with the age of Group 1 less than 20 years (14.6%), Group 2 between 20 and 40 years (46.3%), Group 3 between 40 and 60 years (34.1%) and Group 4 over 60 years (4.9%). Figure 1 shows the relationship between ages and GI bleeding .

### Causes of injuries, injury-admission time and GI bleeding

Road motor vehicles led to injuries of 30 (73.17%) patients, including 6 cases of GI bleeding and the fallings led to injuries of 11 (26.83%) patients, including 4 cases of GI bleeding. The mean injury-admission time was 7.6 hours (range, 2 -24 hours).

### GCS scores and GI bleeding

The patients' distribution in the GCS was 11 mild cases, 10 moderate cases and 20 severe cases. GI bleeding gradually appeared in patients with moderate GCS scores (2 cases) and increased in patients with low GCS scores (8 cases, Figure 2).

### Skull base fracture, hemoglobinemia, hematocrit (Hct), MCTC and GI bleeding

Of the 41 TBI patients, 21(51.22%) had skull base fractures, including 6 (28.57%) cases of GI bleeding.

The mean hemoglobinemia was 125.07 g/L (range, 75 g/L-169 g/L). Twenty-one (51.22%) patients with hemoglobinemia<90 g/L, 5 patients with hemoglobinemia <115 g/L, 3 (12%) patients with Hct>35% and 7 (43.75%) patients with Hct<35% had GI bleeding.

The MCTC classification showed that 28 (68.29%) patients were at score 6, 6 (14.63%) at score 2, and 3 (7.31%) at score 3. Of the 28 patients with score 6 in MCTC, 26 attended the brain surgical operation, and 2 had conservative treatments. Three (7.31%) patients with score 3 developed GI bleeding.

In this study, the mortality rate in the GI bleeding positive group reached 20%. According to the GOS results, the overall mortality rate was 7.31% (3/41), the persistent vegetative state rate was 7.31% (3/41), the severe disability rate was 9.76% (4/41), the moderate disability was 21.95% (9/41) and the good recovery rate was 53.65% (22/41).

### Statistical analysis

**On admission (24 hours)** The concentrations of total cortisol and ACTH had significant differences between the control group and the patients group ($P$<0.01). But there were no statistical differences between the mean ages of the two groups.

The median concentration of patients' ACTH was much higher in the bleeding group (150.0 pg/ml) compared with the control group (28.3 pg/ml) and the non-bleeding group (51.6 pg/ml). The peak concentrations of ACTH and gastrin appeared in the GI bleeding positive group.

The conformity test of the ACTH samples from the GI bleeding negative group has statistical significance ($P$=0.011). Figures 3 and 4 show the differences of mean concentrations of ACTH and gastrin in three groups.

By Spearman Rank correlation test, the severity of injury classified by the GCS showed a positive correlation with the plasma gastrin on admission ($r$=0.312, $P$=0.047) and presented a strong positive correlation with patients' GOS ($r$=0.689, $P$<0.01).

**Dynamic changes** Figures 5 and 6 show the three time-points concentrations of ACTH and gastrin in GI bleeding positive group and GI bleeding negative

group. Tests of the three time-points gastrin samples showed that many comparisons had statistical significance. The results of within subject effects test showed that the difference of three time-points gastrin collection had a statistical significance (*P*=0.000). The results of between subjects effects (Greenhouse-Geisser correction value) test showed that the difference of gastrin concentrations between GI bleeding positive group and control group has a statistical significance (*P*=0.019). The pair wise comparisons test of gastrin samples showed significant differences of all comparisons (α=0.05 and *P*<0.05).

### Regressions

Unifactorial logistic regression analysis of GI bleeding considered GCS ( *OR*=0.284, *P*=0.009), Hct (*OR*=5.704, *P*=0.014) and hemoglobin (*OR*=0.355, *P*=0.014) as the main gastrointestinal risk factors. And the multivariant logistic regression analysis of GI bleeding found that gastrin concentration (*OR*=26.643, *P*=0.045) and Hct concentration (*OR*=5.385, *P*=0.018) were the main risk factors. In this study, the model regression equation we used was as follows:

Ln (P)=3.283*Hct_concentration+1.684*gastrin _concentraion-4.115, [P=0, GI b (-); P =1, GI b (+)]

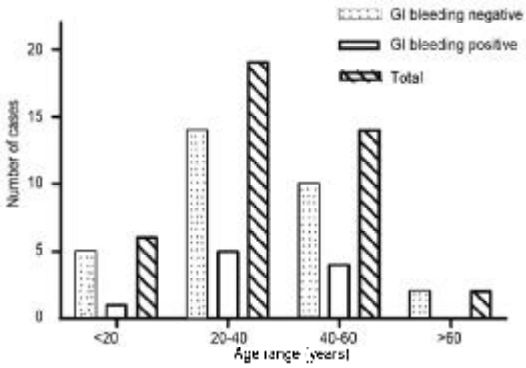


**Figure 1.** Distribution of GI bleeding in four age groups.

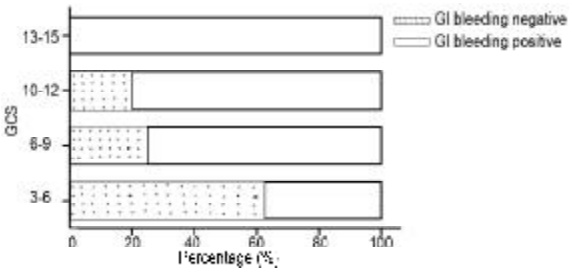


**Figure 2.** Relationship between GCS and GI bleeding in this study.

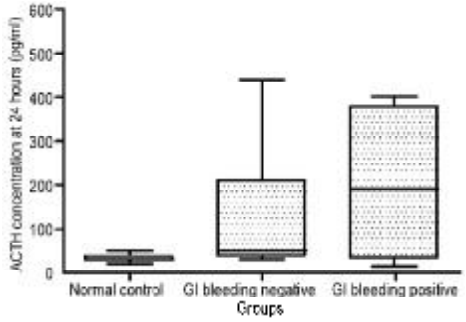


**Figure 3.** Median ACTH concentrations at 24 hours of normal controls, GI bleeding positive group and GI bleeding negative group.

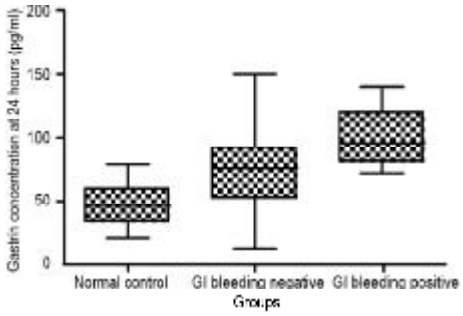


**Figure 4.** Median gastrin concentrations at 24 hours of normal controls, GI bleeding positive group and GI bleeding negative group.

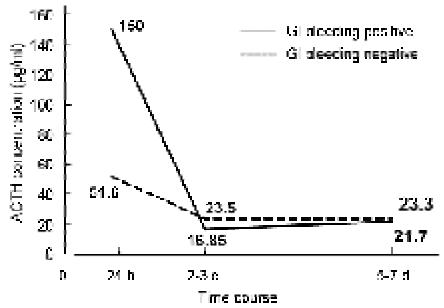


**Figure 5.** ACTH concentrations in GI bleeding positive group and GI bleeding negative group at three time-points.

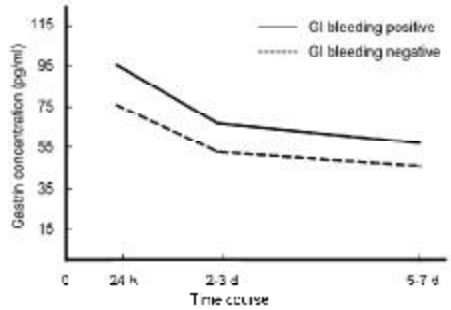


**Figure 6.** Gastrin concentrations in GI bleeding positive group and GI bleeding negative group at three time-points.

## DISCUSSION

Sharples et al[15] found that TBI is the most common cause of death and acquired disability in children and

adults in the developed countries. The characteristics of patients in our study showed that adults over 36 years are the most risky population, with motor vehicles as the major cause of injury.

The mean injury-admission time was 7.6 hours, and the median time was 5 hours (range, 2-24 hours), which is late for the early blood sample collection and early treatment in the longitudinal study. In the emergency care, the best management of patients, especially those with TBI, often starts before the second injury period. In some studies, interleukin-6 appears in bloodstream 1.5 hours after injury and reached the peak 6 hours after injury.[16,17] Using the closed head injury model of TBI, Shohami et al[18] demonstrated significant elevations in plasma cortisol and ACTH at 2 hours and 8 hours after injury as compared with the controls. To get a better result, the treatment given after the peak of the second injury should be specific and not preventive.

Fortunately, for the earlier sample collection, there were 26 (63.41%) patients attending the brain surgery, which covered the delay between injury and admission.

GI bleeding is known to be a severe complication of TBI. Cooke et al[19] described the incidence of overt bleeding to be 4.4% and clinically significant bleeding to be 1.5%. In our trial, GI bleeding happened to 24.39% (10) of patients. The differences of results might be caused by the differences in the methodology of the selection, the criteria, the management and the available treatments.

For critical TBI, accumulation of risk factors seems to increase the risk of bleeding.[13] Some studies demonstrated the relationship between the severity of disease and the incidence of ulcerations and GI bleeding.[20] Moreover, they showed that severe head injuries and GCS score<9 can lead to gastric acid hypersecretion and hemorrhage rate exceeding 17%.[13] In our trial, nearly 40% of patients with GCS score $\leqslant$ 9 developed GI bleeding. Studies have found that respiratory failure and coagulopathy are independent predictors of clinically important bleeding.[2] In our study, low GCS score, low Hct and low hemoglobinemia have been statistically identified as the main risk factors. Correlation analysis found a strong association between GI bleeding and Hct and gastrinemia at 24 hours. A positive correlation between the GCS and the GOS was found.

All studies show the importance of blood volume for the equilibrium of homeostasis. The percentage of blood loss after injury is a strong factor of trauma severity, which determines the rapidity of intervention after injury. Low Hct and low hemoglobinemia present the degree of blood loss, which influences the ischemia status in the gastric mucosa.

Neuroendocrine responses differ in the acute and prolonged phase of critical illness.[21] Endocrine alterations are associated with clinical and neuroradiological measurements of TBI severity. Dimopoulou et al[22] demonstrated that endocrine abnormalities are associated with the extent of brain CT findings as expressed by Marshall's classification. More severe mechanical compression and vascular injuries occur in midline structures, such as the hypothalamus-pituitary complex, thereby leading to endocrine abnormalities. The combined effects of these variables indicate a high grade in MCTC.[23]

By following up 70 TBI patients from 1 month to 23 years after trauma, Lieberman et al[24] found that 52% of patients had endocrine abnormalities and 46% had low baseline. Morning cortisol and hypogonadism were uncommon. In this study, GI bleeding developed with abnormal ACTH concentrations in 24 hours. Low ACTH concentration (<20 pg/ml) occurred at 21.95% of patients.[25] The reference ratio of ACTH/cortisol of the control group was 2.9 (89.76/30.1) and varied with ages, but in our trial, this ratio was only 1.7 (30.1/17.78) with no significant differences in terms of sex and age.

The peak concentrations of ACTH and gastrin were evaluated in the early period after TBI. Within 24 hours after injury, the patients' mean concentrations of ACTH and gastrin were higher compared with the controls. Samples at 2-3 days and 5-7 days demonstrated a gradual decrease. The variation of these hormone concentrations presented by the results of three time-points samples correlates the description of early increase on cortisol concentration during stress by Cernak er al[11]. But the concentrations of ACTH (24 hours) and gastrin (24 hours) showed a difference between the GI bleeding positive group and the GI bleeding negative group. These concentrations in the GI bleeding positive group were relatively higher than those in the GI bleeding negative group, suggesting that the decrease of these hormone concentrations after the early period reflected

good effects of the treatment and a good management of the patients in the NICU. Further studies need to define yet the duration of the peak hormones.

The normal range of plasma gastrin concentration is <100 pg/ml. Patients with high gastrin concentration are supposed to have gastrinoma and Zollinger-Ellison syndrome case of history, but in our study those patients with gastrinoma showed minimal or no rise in gastrin levels,which suggested that high gastrin concentration in the NICU could be another predictive factor of severity.

In this study, the whole mortality rate was 7.31% (3/41), and 20% (2/10) of the GI bleeding patients. The three deaths were all young female adults, at the age of 20, 36, and 38 years, respectively. The MCTC scores were 5 and 6. One patient (MCTC score=5) did not attend the brain surgery. One patient with a skull base fracture was admitted in the hospital 11 hours after injury. Each patient had at least one hypergastrinemia value in different time-points samples and the ACTH concentrations were variable. The three death cases all had different correlated risk factors.

There are some limitations in our study. First the blood samples were taken at varying time intervals following injury because we recruited patients within 24 hours after injury. According to some studies, the hormonal variation increased rapidly during the first 8 hours following injury. It has been documented that the peak concentrations of hormones differ between the acute period and the subacute period. The best samples should be taken from patients who were undergoing the surgery. But these patients usually got more surgical stress, which would affect the measurements of their stress hormones. Second we did not make prospective studies on hemoglobin or Hct. We did not notice the exact time of overt bleeding apparition and its association with the variation of hormone concentrations. Our patients had a similar level of stress and comparable medical status. We could have more precise results in bleeding if we used the microscopical diagnosis of GI bleeding. Thus larger clinical trials should be done to get more information about the disease.

In conclusion, GI bleeding is a severe complication of TBS, with a high incidence and mortality. It was a result of multifactorial stimulations that destroy many basic neuroendocrine systems of the body. This syndrome can be estimated at the early time (within 24 hours after injury).

In this trial, we found many risk factors and one more predictive value (plasma gastrinemia within 24 hours) of this disease. Since GI bleeding might lead to unfavorable prognosis, much more attention should be paid to the prevention and treatment of GI bleeding, especially in TBI patients with risk factors.

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